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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

QIAN, CELINE X

ART UNIT PAPER NUMBER

1636

DATE MAILED: 08/01/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/921,771

Applicant(s)

LI, DEAN Y.

Examiner

Celine Qian

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 1-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 & 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Claims 1-23 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group III in Paper No. 7 is acknowledged.

Accordingly, claims 1-17 are withdrawn from consideration for being directed to non-elected subject matter. Claims 18-23 are currently under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, page 14). Applicant is required to delete all occurrences of embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a blood vessel comprising endothelial cells comprising exogenously supplied polynucleotide encoding a protein that is capable of inducing endothelial

Art Unit: 1636

remodeling in endothelial cells. The specification discloses that arterial-venous identity of endothelial cells in vascular tissue can be changed by introducing a nucleic acid encoding an endothelial remodeling protein into the endothelial cells (page 4-5). The specification the expression of said protein in the blood vessel would induce morphological changes in vein and switch the vein into artery, and said blood vessel can be used in graft for replacement of obstructed vessel (page 3, lines 21-24).

The art at the time of filing teaches that arterial and venous endothelial cells are molecularly distinct from the earliest stages of angiogenesis. The distinction is revealed by either genes that are differentially expressed in endothelial cells of arteries and veins, for example ephrin-B2, EphB4, elastin, and CD34, or genes have a function of allowing endothelial cells to develop distinct artery or vein identities, for example, endoglin or Alk-1. Gene knockout experiments in mice revealed that both endoglin and Alk-1 are essential for arterial development. Homozygous disruption of either of these two genes results in embryonic lethality due to failure to develop arterial network (see Urness et al., 2000, *Nature*, 26: 328-331, and Li et al., 1999, *Science*, 284:1534-1537). Ephrin-B2 expresses only on arteries cells whereas its receptor Eph-B4 only expresses on venous cells (Wang et al., 1998, *Cell*, 93: 741-753). Elastin is a major component of extracellular matrix of arteries and is important in regulating arterial development for its function in controlling proliferation of smooth muscle cell and stabilizing arterial structure (Li et al., 1998, *Nature*, 393: 276-280). CD34 preferentially expresses in early angiogenic arteries rather than venous (Wood et al., 1997, *Blood*, 90:2300-2311). However, none of references teaches that any one of these genes is responsible for all the arterial or venous morphology observed in vivo. Based on gene knockout experiments, disruption of either of

Art Unit: 1636

these genes results in failure of arterial development, indicating that these genes must act in a concerted manner for arterial or venous development. However, development does not necessarily mean remodeling. The prior art does not teach that a terminally differentiated endothelial cell of arterial or venous origin can be reversed by introducing an exogenous nucleic acid encoding a gene involved in the arterial or venous development. In other words, although the genes listed above are important in early blood vessel development, the nexus between expression in an adult differentiated endothelial cell and changing the blood vessel morphology is missing. In addition, it appears not logical to introduce EphB4, a venous specific protein to a vein and expect the vein to display arterial morphology as a result of the protein expression. Therefore, it is unpredictable whether expression of one or more endothelial remodeling gene such as the ones mentioned above is capable of switching arterial-venous identity.

The breadth of the claims is broad. The broadest claim encompasses any blood vessel comprising an exogenous introduced nucleic acid encoding any remodeling gene. Genes capable of endothelial remodeling include several classes of genes some of which are involved in blood vessel formation, development, stabilization, and angiogenesis. The teaching of the specification is limited. The specification only teaches how to use blood vessels that demonstrating arterial property due to exogenous gene expression in venous endothelial cells. The specification does not teach or provide a working example of a single or combination of remodeling gene that are capable of inducing arterial-venous morphological change *in vitro* or *in vivo*. The specification does not teach how to use the blood vessel with exogenous gene expression that does not confer morphological changes to artery. Therefore, in view of lack of teaching from both the

Art Unit: 1636

specification and prior art, one skilled in the art would have to engage in undue amount of experimentation to use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 18-23, the term “polynucleotide encoding a gene” renders the claims indefinite because it is unclear whether the “gene” is a protein or DNA. Polynucleotides conventionally only encode proteins. The term “endothelial remodeling” also renders the claims indefinite because it is unclear what type or which class of genes the applicants are referring to. As discussed above, endothelial remodeling gene include several classes of genes some of which are involved in blood vessel formation, development, stabilization, and angiogenesis. However, the specification appears to refer only to the genes that are capable of changing veins to artery. Applicants need to clarify the claimed subject matter.

Regarding claim 22, the term “or both” renders the claim indefinite because it is unclear how one gene can encode both endoglin and Alk-1. Since the parent claim recites only “a gene,” and it is neither disclosed in the specification or in prior art that the gene encodes endoglin can also encode Alk-1.

Regarding claim 23, the recitation “the gene encodes one or more of ephrin-B2...” renders the claim indefinite because it is unclear whether the gene encodes one or more of the

Art Unit: 1636


genes individually or combination of different genes. It is also unclear how one gene can encode one or more protein since neither the specification nor the prior art teaches these proteins are encoded by the same gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
July 29, 2002


REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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